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⑭発明の名称　擬似生体構造物

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明　細　書

1．発明の名称　擬似生体構造物

2．特許請求の範囲

けん化度95モル%以上、平均重合度1,000以上のポリビニルアルコールを含み、且つ、該ポリビニルアルコールの濃度が8wt%を超え、50wt%以下の水溶液を、任意形状の成型用鋳型へ注入後、これを－10℃以下の温度に冷却・固化・成型し、次に、これを解凍する一連の凍結・解凍操作を反復して累積凍結回数を1～8とすることにより得られる高含水ゲル、もしくは、上記冷却・固化体を融解させることなく、これに、脱水率（固化・成型体の重量減少率）3wt%以上の真空・部分脱水を施すことにより得られる高含水ゲルからなる電磁波治療用または超音波治療用ファントム（擬似生体構造物）。

3．発明の詳細な説明

<産業上の利用分野>

本発明は擬似生体構造物、特に電磁波または超音波を用いる医療（治療）の遂行に必要なファントム（擬似生体構造物）に関する。

<従来の技術及び問題点>

従来より、電磁波（加温）療法、放射線治療、超音波療法などの遂行に必要なファントム（擬似生体模型）構造物として、動物の新鮮断層または、これを模したこんにゃく、ゼラチン（ゼリー）、寒天、ゴム、澱粉糊などが提案され、一部は既に実用されているが、なお多くの難点が指摘されている。

まず、これらの電磁波または超音波を用いる治療におけるファントム（擬似生体構造物）の必要性を下記に要約する。

放射線を病巣へ到達させるにあたり、照射線源と病巣間に介在する正常（健常）組織を無視できない。介在組織が平坦で、均一厚みを呈する場合は、介在組織による放射線の減衰をあらかじめ考慮し、病巣領域へ、予測どおり所望線量を到達せしめることができる。しかし、体表面は一般に平坦でないため、上記介在組織を均等減衰帯（一定の厚みの平板）として近似できず、照射治療遂行

上の難点が生じる。この難点を克服するため、体表面（介在組織表面）の平坦化が図られる。これには体表面近傍を圧縮変形せしめる平坦化法も一応は考えられるが、体表面組織の変形成形（非侵襲平坦化）に限度があり（その効果は乏しく）、むしろ体表面（皮膚面）上へ擬似生体組織を補い、これを自在に成形、構築して、病巣と線源を結ぶ方向に対する垂直平面を形成させる方式が採られる。したがって、この場合、擬似生体組織としては、任意成形可能で、体表面に密着しうる、しかも生体組織と同等の放射線減衰効果を示す材料が望まれる。

また、放射線の体内減衰状況の詳細をあらかじめ検討するための模型として、生体組織同様の放射線特性の素材が望まれる。超音波を用いる治療（温熱療法）において、超音波放出端子（探触子）を体表面へ接触させるにあたり、探触子・皮膚面（体表面）間に介在する少量の気泡（空気）により、超音波の大部分が反射されるため、探触子・皮膚面（体表面、組織表面）間に、空気排除材を介在させる手法が採られるが、この空気排除材として、探触子・皮膚面の双方に密着し、しかも生体組織と同等の超音波特性（インピーダンス）を有する素材が望まれる。

超音波、ラジオ波、マイクロ波などを照射する癌の温熱療法において、照射時の体内病巣温度を、４１．５～４３℃に所定時間維持する必要があるが、照射条件（周波数、照射時間）と体内各部位の温度上昇との関係をあらかじめ知る必要上、生体模型が望まれ、この場合、生体組織と同等の熱特性を示す素材が切望されている。

このように、超音波または電磁波を用いる治療における擬似生体構造物の必要性は周知である。擬似生体構造物素材としては、屠殺直後の動物組織が挙げられるが、このような新鮮な組織を、所望の都度、即刻入手するのは困難で、またこれを入手後、冷所に保存しても、その電磁波物性または超音波物性が激しく変化する(H.F.Bowman; Ann. Rev. Biophys. Bioeng., 4,43(1975), F.K.Storm et al.;Int.J.RediationOncology Biol.Phys., 8, 865(1982)、関谷富男他(柄川順編)、"癌・温熱療法" p.39(1982)篠原出版、田中邦男他、北大応電研報, 29,(3)174(1977)、山田芳文他、北大応電研報,29,(3)184(1977)、R.V.Damadian; US 3,789,832(1974))．したがって、生体組織類似物性の天然物または人工物が探索されてきた。

一般に、生体組織は電磁波物性および超音波物性が水に似ることから(斉藤正男："生体工学" p.19,20,21,24,25(1985)コロナ社、菊池喜充；"超音波医学" p.7, p.69(1980)医学書院)、水または高含水ゲルが擬似生体構造物素材として提案された。例えば、放射線照射において、照射面平坦化の目的から、皮膚面に水嚢(水封入袋)を置き、また電磁波加熱、超音波加熱等においても、空気排除(反射・散乱防止、インピーダンス整合)の目的から、同じく皮膚面に水嚢が置かれるが、この場合、水嚢は変形、移動し易く、安定操作に難がある。この欠点を克服するため、ゼリー、こんにゃく、寒天などの高含水ゲルが提案された。これらは９６～９８％の水分を含むことから、生体組織に類似の物性を示し、しかも一応の形状保持性をも具えるが、ゼリー（ゼラチン）は軟弱で、形くずれし易い（近田伸一（日本電子機械工業会編）、"医用超音波機器ハンドブック" p.242(1985)コロナ社)。寒天も、もろくて破損し易く、こんにゃくは、製作後の離漿に因る変形（収縮）が激しい。また、これらはいずれも、生体組織（軟組織・水分７０～８０wt％）に比し、含水率が過大であり、この点においても、必ずしも満足できるものではない。生体類似性を更に高める目的から、これらの水の一部をｎ－プロピルアルコール、グリセリン、ポリエチレングリコール、炭酸ナトリウム、グラファイト粉などに置き換える試みもあるが、このような調整を図るには、寒天、こんにゃく等の天然物の品質が不安定で、統一規格品の安定供給に難があることも指摘されている（近田伸一（日本電子機械工業会編）、"医用超音波機器ハンドブック" p.242(1985)）．

前記ゼラチンの形くずれを防ぐため、ホルマリン、グルタルアルデヒドなどにより架橋する試み

もあるが(E.L.Madsen et al.; Ultrasound in Med.Biol.,8,(4)381(1982)、E.L.Madsen et al.; Mag.Res.Imag.1,135(1982)、E.L.Madsen et al.; Am.Assoc. Phys. Med.,5,391(1978))、この場合、不均質ゲル化(架橋)を招き、一定品質の形成品は得難い。カラゲナン、アルギン酸などの多糖類の高含水ゲルも、寒天同様、機械的強度に劣る。

著名な合成系高含水ゲルとしてのポリアクリルアミドは、含水率を生体等価(70～85%)に調整しうる利点はあるが(山崎達男他;放射線研究、13,92(1983))、ゲル化(ラジカル架橋)が均一に進行し難く、均質成形品は得られない。また、このゲル自体がもろく、ピンセットなどを用いて取り扱う場合に破損し易い。

このように、水嚢及び天然系ゲル、合成系ゲルのいずれにも適切な構造物素材を求め難いことから、むしろ水中へ患部を浸す水浸法が採用されており、例えば乳癌の場合、腹臥位において、下垂乳房を水槽中へ浸すことにより、乳房(表面)近傍から空気泡を確実に排除し、ここへ超音波などを照射する。この水浸法は、乳房、四肢、腹部、胸部、頸部に適用しうるものの、大規模な水槽を要するなど、実際の操作に不便であるほか、顔面(頭部)、眼球、術中諸臓器などに適用し難い。

<発明の目的>

本発明は、生体組織と同等の超音波物性と電磁波物性を具え、柔軟で、しかも非流動性の、破損し難い高含水ゲルからなる物理治療(電磁波または超音波を用いる治療)用擬似生体構造物素材を提供する。

<問題点を解決するための手段>

本発明によれば、けん化度95モル%以上、平均重合度1,000以上のポリビニルアルコールの濃度が8wt%を超え、50wt%以下の水溶液を、任意形状の成型用鋳型へ注入後、これを－10℃以下の温度に冷却・固化・成型し、次にこれを解凍する一連の凍結・解凍操作を反復して累積凍結回数を1～8とすることにより得られる高含水ゲル、もしくは、上記冷却・固化体を融解させることなく、これに、脱水率(固化・成型体の重量減少率)3wt%以上の真空・部分脱水を施すことにより得られる高含水ゲルからなる物理治療用擬似生体構造素材が提案される。

以下、本発明を更に詳細に説明する。

本発明では、物理治療用擬似生体構造物素材を、次に述べる特定処方による高含水ゲルを用いて製作する。

本発明に用いるポリビニルアルコールは、そのけん化度が、95モル%以上、好ましくは98モル%以上を要する。また、ポリビニルアルコールの重合度は1,000以上を要する。

本発明では、まず、前述のポリビニルアルコールを含む水溶液を調合する。ポリビニルアルコールの濃度としては、8wt%を超え50wt%以下とする。

本発明においては、上記ポリビニルアルコール水溶液を人体模型または人体局部体表面の形状に適合しうる所望の成形に適した鋳型へ注入し、冷却、凍結後、これを解凍することにより、本発明に供しうる高含水ゲルを得ることができる。また、更に機械的強度に富む素材を望む場合は、上記凍結・解凍操作を反復して、累積凍結回数を2～8とすることにより、本発明に供しうる高含水ゲル(ゴム)を得ることができる。累積凍結回数を高めるとともに、得られる高含水ゴムの硬度も向上するが、累積凍結回数9以降は、その効果がほぼ消失すること(南部昌生、高分子加工、32,523(1983))から、上述の2～8が経済的である。

本発明では、前述の冷却・凍結後、これに解凍・再凍結操作を反復する替りに、凍結体を解凍させることなく、真空・部分脱水を施してもよい。この場合、脱水率(冷却・固化ゲルの重量減少率)が高まるとともに、ゲルの機械的強度も向上するが、脱水率を特に著しく高めて強固なゲルを得ることは必要でなく、脱水率3wt%以上、好ましくは3wt%以上で35wt%以下にとどめるのが、ゲルの形態保持性、加工性の観点から好ましい。

ここで言う真空・部分脱水は減圧で若干脱水することで、減圧の度合は特に限定されないが、たとえば1mmHg以下、好ましくは0.1mmHg以下、さ

らには0.08mmHg以下で行なうことができる。前記成型用鋳型としては、前述のとおり、生体模型あるいは局部体表面の形状に適合しうるなど、所望の形状が得られることの他に、特に制約はないが、マイクロ波、ラジオ波、γ線、X線、中性子、レーザー光線、超音波などを用いる治療の実情に応じ、適宜、厚み(均一度または厚みの分布)、寸法、形状などを選定できる。

本発明においては、各種生体組織の含水率に準じ、各種のゲルを得ることができる。ゲル含水率は、当初のポリビニルアルコール水溶液（または懸濁液）の調合組成に依存する。ポリビニルアルコール水溶液（または懸濁液）を凍結後、これに部分脱水を施した場合、この脱水量を考慮することにより、ゲル含水率が算出される。部分脱水操作を省略し、単なる凍結・解凍（またはその反復）により得たゲルについては、当初のポリビニルアルコール水溶液（または懸濁液）が、そのままゲル化していることから、容易にゲル含水率が算出される。

したがって、本発明においては、各種生体組織の含水率、即ち皮膚（５１～６９％）、尿管（５８％）、項靭（５８％）、アキレス腱（６３％）、舌（６０～６８％）、前立腺（６９～７６％）、水晶体（６７～７０％）、肝臓（７０～７７％）、胃（８０％）、脾臓（７５％）、小腸（８０％）、骨格筋（７９～８０％）、子宮（８０％）、胸腺（８２％）、膀胱（８２％）、腎臓（７８～８１％）などに準じ、それぞれの擬似生体構造物が製作され、それらの電磁物性（比誘電率(透電率)、導電率、熱伝導度、比熱、硬度）及び超音波物性（密度、音速）もまた、それぞれの生体組織にほぼ合致する特長がある。上記に列挙した諸物性の重要性は周知のとおりであるが、密度（生体軟組織0.98×10^{3}～1.1×10^{3}〔kg m^{-3}〕）は、X線の透過性を左右するほか、熱拡散係数と反比例する重要因子であり、超音波速度、超音波の透過、反射、減衰をも支配する（関谷富男他（柄川順編）；“癌・温熱療法”p.32(1982)篠原出版、H.S.Ho et al.; Trans. Microwave Theory. Tech. MTT19, 224(1971), J.B.Leonard et al,; IEE Trans. Biomed. Eng.,BME-31,533(1984), F.W.Kremkau(小林利次訳)；“超音波診断の原理と演習”(1981)金芳堂)。硬度（体積弾性率、生体軟組織２．６×１０^{9}Ｎｍ$^{-2}$）は、やはり超音波の反射、透過、減衰を支配し、超音波速度が体積弾性率の１／２乗に比例することなどがよく知られている。

比誘電率（生体軟組織１０ＭＨｚ領域で６４～２００、１ＧＨｚ領域で３０～８０）は電磁波の減衰、反射、インピーダンスを支配し、例えば、発熱損失量と比例すること、電磁波透過深度が比誘電率の１／２乗に比例することなどが著名である(柄川順編；“癌・温熱療法”p.21,p.63(1982))。

導電率（生体軟組織１０ＭＨｚ領域で0.5～0.9、１ＧＨｚ領域で１～２、１０ＧＨｚ領域で１０〔ohm^{-1}m^{-1}〕）は、やはり電磁波の減衰、透過性、インピーダンスを支配し、例えば透過深度は導電率の－１／２乗に比例する。

熱伝導度（生体軟組織１ＭＨｚ領域で0.5～1.3〔Jm^{-1}s^{-1}K^{-1}〕、１ＧＨｚ領域で0.48～0.66〔Jm^{-1}s^{-1}K^{-1}〕）は、電磁波照射時の生体の発熱と熱拡散を支配し、この場合の生体組織温度は熱伝導度の１／２乗に比例する。

比熱（生体軟組織3.2～3.7〔Jg^{-1}K^{-1}〕）も、同じく、発熱、熱拡散を支配し、生体組織温度は比熱の－１／２乗に比例する。

生体軟組織の上記諸項目の物性値は、いずれも、生体組織中の含水率により必然的に決定されている（生体組織の諸物性が概略、水に近似する）ことがよく知られている（斉藤正男；“生体工学”p.19,p.20,p.27(1985)コロナ社、菊池喜充；“超音波医学”p.7,p.69(1980)医学書院)。本発明に用いる擬似生体構造物素材も、多量の水を含むことから、上記諸物性をほぼ満足するが、本発明素材においては、生体軟組織の含水率（５１～８２wt％、通常７０～８０wt％）に合致させうることから、単なる純水の場合より、更に生体類似性に優れる。もっとも、生体内には、脂肪に富む組織の存在することも周知である。脂肪分に富む組織を模すには、当初のポリビニルアルコール水溶液

へ脂質を混入して均一に分散させれば良く、例えば含水率40%の脂肪組織を模すには、含水率80%のポリビニルアルコール水溶液へ等量のレシチンまたはトリステアリンなどを分散させる。更に脂肪分の多い組織を模すには、脂肪による擬似生体構造物(ゲル)の形態保持性低下を避ける観点から、モノステアリン、トリステアリンなどの固形脂肪を加熱液化後、70℃以上に加熱したポリビニルアルコール水溶液へ添加して、均一に懸濁させ、次に本発明の凍結操作を施す。これにより、含水率15〜30%の脂肪組織相当の擬似生体構造物が得られ、しかも、その電磁波物性及び超音波物性は、生体脂肪組織にほぼ合致する。

本発明においては、このようにして得た含水率の異なる人体諸組織擬似構造物を互いに張り合わせ(て連結す)ることができる。この場合、接着剤としてシアノアクリレート系を用いることもできるが、好ましくは、接着面に、所望含水率のポリビニルアルコール水溶液を塗布して接合後、これに凍結・解凍を施すのが至便である。

本発明においては、成型用鋳型をあらかじめ所望どおり製作することにより、適切な形状のゲルが得られるほか、任意形状のゲルを得た後、これをはさみまたは鋭利な刃物により裁断して、所望形状とすることも差支えない。また、あらかじめ、鋳型内に人骨などを埋め込むか、あるいは生成したゲルへ灼熱した鉄製丸棒を差し込むことにより得られる腔路へ人骨などを挿入して、生体骨格を含む組織を模すことができるほか、ゲル内に気管、食道、胃、膀胱、肺、鼻腔、口腔、血管、尿管、尿道などを模した空間または水分貯留腔を設けることができ、空気、貯留液、血流などによる電磁波または超音波の反射、散乱、吸収、透過、多重反射状況を検討するための生体等価モデルとしての要件をも充足する。

本発明においては、ポリビニルアルコール単一成分がゲル素材(ゲル化成分)として用いられる。しかし、ポリビニルアルコールのゲル化を阻害しない成分を、必要に応じ共存させることは、前述の油脂添加例に示すとおり、本発明に差支えなく、その共存量としては、例えばポリビニルアルコールの1/2量以下とすることができる。

上述の、ポリビニルアルコールのゲル化を阻害しない成分としては、例えばイソプロピルアルコール、グリセリン、プロピレングリコール、エチルアルコールなどのアルコール類、カゼイン、ゼラチン、アルブミン等の蛋白質、レシチン、モノステアリン、トリステアリンなどの脂質、グルコース、寒天、カラゲナンなどの糖または多糖類、p−ヒドロキシ安息香酸ブチル、フタロシアニン青、フラバンスロンなどの有機化合物、ニッケル塩、銅塩、マンガン塩、鉄塩、グラファイト、活性炭、シリカ・アルミナ、ゼオライト、けい酸カルシウムなどの無機化合物、無機塩、有機酸塩などのほか、電磁波物性の微調整剤として周知の、ポリエチレン粉、アルミニウム粉、アセチレンブラック、炭酸ナトリウム、食塩など(A.W.Guy; IEEE Trans. Microwave Theory Tech., MTT-19, 205(1971)、J.B.Leonard et al.; IEEE Trans. Biomed. Eng., BME-31, 533(1984)、F.K. Storm et al.; Int.J.Radiation Oncology Biol.Phys. 8, 865(1982)、E.L.Madsen et al.; Med. Phys. 5, 391(1978)、M.Michele et al.; Radiology, 134, 517(1980)、P.E.Schuwert; Ultrasonics, 275(1982)、日本電子機械工業会;"医用超音波機器ハンドブック"(1985)コロナ社)をも挙げることができる。

本発明の擬似生体構造素材にこれらを配合するには、これらを、そのまま、または水溶液あるいは懸濁液としてあらかじめポリビニルアルコール水溶液へ添加後、攪拌して均一に分散させ、しかる後、前述の凍結及びその後の処理を施すことができる。

<発明の効果>

本発明の、擬似生体構造物素材は、50〜92wt%に及ぶ水分を含み、皮膚、項靭(水分58〜61%)から、肝臓、膀胱(水分78〜82%)に至る各種生体組織の含水率を包括しうる。

本発明の擬似生体構造物素材はこのように、多量の水を含むにもかかわらず、37℃においても

形態保持性を有し、所望形状に成型し、保存することができる。

本発明の擬似生体構造物素材は、多量の脂肪を含有することができ、含水率の低い生体脂肪組織を模すことが可能である。

本発明の擬似生体構造物素材は含水率を同じくする生体組織にほぼ合致する物性（比誘電率、導電率、密度、熱伝導度、比熱、硬度）を示すことから、電磁波、超音波などを用いる物理治療（X線照射、γ線照射、超音波照射、中性子照射、レーザー光照射、ラジオ波照射、マイクロ波照射）における生体模擬構造物素材としての要件を充足する。

本発明の擬似生体構造物素材は、柔軟性と可逆弾性に富み、複雑な形状の体表面または術中の臓器表面に合わせて成型するかぎり、これらの表面に良く密着しうるうえ、生体軟組織類似の機械的強度をも具えることから、所定部位へ反復貼布して使用できる。

本発明の擬似生体構造物素材は、クロルヘキシジン、オスバンなどの消毒液またはγ線照射により滅菌され、これによる素材の破壊、劣化をきたさないことから、皮膚表面はもちろんのこと、術中諸臓器にも貼用することができる。

本発明の擬似生体構造物素材は、単にポリビニルアルコール水溶液に、低温領域の熱履歴を与えること、あるいは凍結・減圧処理することにより容易に得られ、生体組織に有害な酸、アルカリ、その他の化学試薬、架橋試薬などを全く用いない。したがって、製品から有害物を除くための多大の労力を要せず、しかも、生体組織に対して不活性で、たとえ長期間生体内に埋植しても、周囲組織に異物反応、細胞浸潤、炎症などを認めないことから、皮膚表面はもちろんのこと、術中諸臓器にも長期反復貼用できる。

本発明の擬似生体構造物素材は、内部に任意形状の腔を設けることができ、人骨、獣骨、プラスチック製円筒、チューブなどを埋め込むこともできるため、骨格組織、管腔組織を模すことも可能である。

＜実施例＞

以下本発明の実施例につき説明する。なお、％の表示は重量基準による。

実施例1

平均重合度２，０００、けん化度９９モル％のポリビニルアルコールの２９％水溶液(ＮａＣℓ ０.９％）を、直径１５cm、高さ１２cmの円柱成型用鋳型へ注入後、２回の凍結・解凍を施して得た高含水ゲルの含水率（７０～７１％）がヒトの肝臓（水分７０～７７％）、水晶体（６７～７０％）、前立腺（６９～７６％）に近いことを確かめた。

この試料につき、電磁波物性を測定し、屠殺直後（１時間以内）のイヌの肝臓の場合（〔　〕内）及び純水の場合の値（（　）内）と対比したところ、導電率($\mathrm{ohm^{-1}m^{-1}}$、10MHz) 0.7〔0.6〕(1.5)、誘導率(10MHz)70〔64〕(79)、密度〔$\mathrm{kg\,m^{-3}}$〕1,040〔1,030〕(1,000)、熱伝導度〔$\mathrm{J\,m^{-1}s^{-1}K^{-1}}$〕0.8〔0.7〕(0.6)、定圧比熱〔$\mathrm{J\,g^{-1}K^{-1}}$〕3.7〔3.5〕(4.2)、体積弾性率〔$\mathrm{dyne\ cm^{-2}}$〕$2.5\times10^{10}$〔$2.6\times10^{10}$〕($2.0\times10^{10}$)であり、生体軟組織とよく合致した。

実施例2

平均重合度１，０００、けん化度９８モル％のポリビニルアルコールの18.6％水溶液３１４ｇを、厚さ１cm、直径２０cmの円板成型用鋳型へ流し込み、これを－３０℃に冷却して得た凍結体を、0.1 mmHgの減圧下に、水分２２ｇを除去した後、室温に戻し、含水率８０％の円板状ゲルを得、密封容器に保管した。この含水率は、ヒトの骨格筋、小腸、胃、子宮、腎臓などの含水率（７８～８１％）とほぼ合致する。

次に、この円板をポリエチレン・フィルム製袋に収めて密封し、３Ｍｒａｄのγ線滅菌を施した後、開封し、その一部裁断片（１０ｇ）をブイヨン培地へ移し、７日間３７℃で培養を試みだが、微生物は検出されなかった。他の一部裁断片（４０×４０×１０mm）につき、密度を測定し３７℃において、1.03×10^3〔$\mathrm{kg\,m^{-3}}$〕を得た。これは、純水より若干高く、生体軟組織(1.03×10^3 $\mathrm{kg\,m^{-3}}$)に合致した。次に、この試料中の音響伝

播速度を、水中超音波全反射角検出方式により求めたところ、純水中の音速(1,500〔ms^{-1}〕)よりわずかに高く(1,600〔ms^{-1}〕)、生体軟組織（肝1,600、骨格筋1,600、腎1,560、皮膚1,600〔ms^{-1}〕)の場合とよく合致した。したがって、音響インピーダンス（密度×音速）は、1,648×10^3〔$kgm^{-2}s^{-1}$〕であり、生体軟組織（1,600～1,700×10^3〔$kgm^{-2}s^{-1}$〕)とよく整合する生体等価素材である。シリコーン・ゴム（1,100×10^3）、ポリスチレン(2,460×10^3)、ブタジエン・アクリロニトリルゴム（2,000×10〔$^3kgm^{-2}s^{-1}$〕）などのインピーダンスが生体組織の値と著しく相違するのに反し、上述の本発明の擬似生体構造物素材の利点が明白である。

次に、上述の裁断片につき、放射圧基準の超音波出力を測定し、減衰（吸収）係数3dBcm^{-1}(5MHz)を得た。この値は、純水の場合(0.3dBcm^{-1})に比し、はるかに生体軟組織の値（肝3dBcm^{-1}、腎4.5dBcm^{-1}）に近く、天然ゴム（155）、シリコーン・ゴム（0.8）、ブタジエン・アクリロニトリルゴム（70dBcm^{-1}）などと比較しても、本発明の擬似生体構造物素材の利点が明白であった。

実施例3

平均重合度2,600、けん化度99モル%のポリビニルアルコールの25%水溶液を、直径30cm、高さ30cmの円柱成型用鋳型へ注入し、－40℃において凍結後、解凍を施し、高含水ゲルを得た。その弾性率（10^5Nm^{-2}）は0.4で、平滑筋類似の柔軟性を示し、可逆自在変形性に富むにもかかわらず、50kgcm^{-2}の加圧下に30分保持しても形くずれを招かず、寒天、カラゲナンが容易に圧潰するのと対照的であった。また、その引張り強度は30kgcm^{-2}であった。

実施例4

実施例3に準じて、厚み0.3mmの高含水ゲル膜（30×30mm）を10枚製作した。

これらをクロルヘキシジンを用いて滅菌後、無菌的に生理食塩水により洗浄し、その1枚をウサギ背部皮下に16ヵ月埋植したが、生体組織に炎症、細胞浸潤などの異物反応は見られず、結合組織の過剰増殖も見られなかった。

同じく、雑種成犬を全身麻酔下に挿管し、調節呼吸下に、左第4肋間を開胸して心膜を2cm切開し、この欠損部へ、前記滅菌済試験片をテフデック糸により連続縫合した。1年後の解剖結果、本発明の高含水ゲル周辺になんら異常なく、同じく成犬開胸部位の胸壁に縫着した場合にも、17ヵ月所見では、異物反応・癒着などは全く無かった。

家兎（体重2.5kg）の膝関節内側面を縦方向に3cm切開し、大腿四頭筋内側面を縦切開して膝蓋骨を外側へ脱臼させ、膝関節を屈曲させて関節前部の脂肪組織を切除し、交差靭帯の切断後、後関節嚢以外の関節嚢および半月板を切除する。次に大腿骨関節軟骨を削除し、この軟骨に替えて、前記滅菌済試験片を大腿骨関節面へ挿入・固定後、膝関節150度屈曲位において大腿上部から足部までギプス包帯を施し、4週後にこれを除いた。この時点において、関節には軽度の腫脹を認めたが、発赤・局所熱感は無く、一次性癒合も良好で、分泌液は見られず、膝関節は約120度屈曲位をとり、保護跛行を示す。他動的可動範囲は150～90°であった。組織標本につき、ホルマリン固定、パラフィン包埋、ヘマトキシリン・エオジン染色、マロリー・アザン染色を施し、鏡検の結果、大腿骨造形関節面は結合組織により被覆されており、挿入試料による反応性骨質増殖と骨髄腔内炎症はいずれも認められなかった。これらの諸所見から、本発明の高含水ゲルの生体適合性の良いことが確かめられた。

ラボナールの静注による全身麻酔を施こした体重17kgの雑種成犬の頭皮を脱毛後、右頭頂部に7cmの縦皮膚切開を加えて側頭筋を剥離し、次に、ドリルを用いて頭頂骨に穿孔し、骨鉗子を用いて鶏卵大の骨欠損を設け、1.5×2cmの硬膜切除を加え、この部分へ前記ヒドロゲル（高含水ゲル）膜を当て、四隅を縫合後、筋縫合と頭皮縫合を施した。

8ヵ月後の犠牲死体から、ヒドロゲル膜及びそ

の周囲硬膜と脳実質を剔出し、肉眼観察及びヘマトキシリン・エオジン染色による光学顕微鏡観察を実施したが、ヒドロゲル膜と脳表面との癒着は認められなかった。また、ヒドロゲル表面は被覆様組織により包囲されていたが、軟膜への癒着はほとんど認められず、細胞浸潤及びグリア細胞の増殖なども見られなかった。

ペントバルビタールの静脈麻酔を施した体重13kgの雑種成犬を開胸し、左室側心膜に縫い代を残す程度に及ぶ広範囲の切除を加え、ここに、前記ヒドロゲル膜による組織欠損部補填を施した。

8ヵ月後の犠牲死体から得られる上記補填部の切除標本につき、肉眼、光学顕微鏡及び走査型電子顕微鏡により観察した結果、心臓側における補填部との癒着は全く認められず、ヒドロゲル膜表面は、内皮様組織により被覆され、平滑であった。病理組織学的にも細胞反応は無く、心臓側に薄い内皮様組織が見られた。

体重15kgの雑種成犬につき、開胸後、横隔膜筋性部に欠損を作製し、前記のヒドロゲル膜により補填した。8ヵ月後の犠牲死体から得た補填部切除標本を観察した結果、補填部と肺との癒着は見られなかった。また、試料は薄い膠維組織に包被されており、組織反応は見られなかった。

実施例5

平均重合度1，200、けん化度99％のポリビニルアルコールの15％水溶液を曲率半径8㎜、厚さ（0．2㎜均一）、直径13㎜の曲膜成型用鋳型へ注入後、2回の凍結・解凍を施して得た成型品をボランティアの眼球角膜に10時間装着し、脱着後、角膜にフルオレスチン染色を施こしたのち、細隙燈顕微鏡により観察したが、角膜染色部分は見当らなかった。即ち、本発明擬似生体構造物素材が眼球角膜に不活性で、生体適合性に優れることが明白で、実施例4の知見と併せて、必要に応じ、生体組織に接触させて用いるのに適していることが明らかである。

手続補正書(自発)

昭和61年6月11日

特許庁長官　宇賀道郎　殿

1．事件の表示

昭和61年　特許願　第91228号

2．発明の名称

擬似生体構造物

3．補正をする者

事件との関係　特許出願人

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5．補正の対象

明細書の「発明の詳細な説明」の項

6．補正の内容

明細書を下記のとおり補正する。

頁	行	補正前	補正後
3	15	望まれる。	望まれる。更には、
4	20	RediationOncology	Rediation Oncology
7	5	形成品	成形品

61.6.11

【公報種別】特許法第１７条の２の規定による補正の掲載
【部門区分】第１部門第２区分
【発行日】平成５年（１９９３）１２月１４日

【公開番号】特開昭６２－２４９６４４
【公開日】昭和６２年（１９８７）１０月３０日
【年通号数】公開特許公報６２－２４９７
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手続補正書

平成 5年 3月 1日

特許庁長官　殿

１．事件の表示
昭和６１年 特 許 願 第９１２２８号

２．発明の名称
擬 似 生 体 構 造 物

３．補正をする者
事件との関係　特許出願人

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５．補正の対象
(1) 明細書の「特許請求の範囲」の項
(2) 明細書の「発明の詳細な説明」の項

６．補正の内容
別紙のとおり

１．本願明細書の「特許請求の範囲」を下記のとおり補正する。

『特許請求の範囲

けん化度９５モル％以上、平均重合度1,000 以上のポリビニルアルコールを含み、且つ、該ポリビニルアルコールの濃度が８wt％を超え、５０wt％以下の水溶液を、任意形状の成型用鋳型へ注入後、これを－１０℃以下の温度に冷却・凍結・成型し、次に、これを解凍する一連の凍結・解凍操作を反復して累積凍結回数を１～８とすることにより得られる高含水ゲル、もしくは、上記冷却・凍結体を解凍させることなく、これに、脱水率（凍結体の重量減少率）３wt％以上の真空・部分脱水を施すことにより得られる高含水ゲルからなる電磁波治療用または超音波治療用ファントム（擬似生体構造物）．』

２．本願明細書第８頁第１６行「固化」を『凍結』に、同第１９行「固化体を融解」を『凍結体を解凍』に、同第２０行「固化・成型体」を『凍結体』にそれぞれ補正する。

３．本願明細書の第１０頁第９～１０行「解凍・再凍結操作」を『凍結・解凍操作』に、同第１２行「冷却・固化ゲル」を『凍結体』にそれぞれ補正する。

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(54) Material for simulating living tissue.

(57) A material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies is provided. The material comprises a hydrogel having a high water content. The hydrogel is prepared by the steps of casting an aqueous polyvinyl alcohol solution into a mold, cooling the cast aqueous solution to obtain a cooled frozen mass and thawing the cooled frozen mass. The cooling and thawing steps may be repeated up to eight cycles. The hydrogel is also prepared by subjecting the cooled frozen mass to a partial dehydration step in vacuum.

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Material for Simulating Living Tissue

BACKGROUND OF THE INVENTION:

Field of the Invention;

The present invention relates to a material for simulating a living tissue, and more particularly to a material for forming a phantom for applying medical treatment or therapy using electromagnetic or ultrasonic waves.

Related Art Statement;

A fresh cut piece of an animal tissue or a material for simulating a living tissue made of, for example, KONNYAKU (devil's tongue), gelatin (jelly), agar, rubber or starch paste, has been proposed to prepare a phantom (a model for simulating a living tissue) used in the practice of electromagnetic wave therapy (thermal therapy), radiotherapy or ultrasonic wave therapy. Although some of these known materials have been used practically, they have many problems.

A phantom simulating a living tissue is required for the therapy, in which electromagnetic waves or ultrasonic waves are used, for the following reasons.

When a lesion site is irradiated with a radioactive ray, the normal or healthy tissue present between the source of radioactive ray and the lesion site cannot be neglected. If the living tissue interposed between the source of radioactive rays and the lesion site is flat and has an uniform thickness, the attenuation of the radioactive ray by the interposed tissue can be estimated to control the radioactive ray so that the lesion site is irradiated with a desired dosage of radioactive ray. However, since the surface of the patient body is generally not flat and even, the interposed tissue cannot be closely estimated as an equivalent attenuating region (a flat plate-like region having a uniform thickness) to pose a problem for execution of radiotherapy. In order to overcome the problem, it has been tried to flatten the body surface or the surface of the interposed tissue. Although a method of compressing the body surface to deform the vicinity of the body surface has been adopted as a tentative measure, the deformation of the body surface tissue (flattening of the body without invading the tissue). is limited and only a limited effect is obtained by such a measure. Accordingly, it is a common practice to apply a material for simulating the living tissue on the surface of the body or skin, followed by molding the living tissue simulating material to have desired shape and dimensions to provide a flat surface which is normal to the direction from the lesion site to the source of the ray. Thus, there is a demand for a material which can simulate a living tissue and moldable to have a desired shape to be closely fitted on the surface of the patient's body and which exhibits a radioactive ray attenuation equivalent to that of the living tissue.

It is also desired that the material has a characteristics under the irradiation of a radioactive ray similar to those of the living tissue in order to be a model for examining the details of the attenuation of the radioactive ray in the living body. In the ultrasonic wave therapy (thermal therapy), a major portion of the ultrasonic waves is reflected by a small amount of air bubbles present between the surface of the skin and a probe or terminal for discharging ultrasonic waves when the probe or terminal contacts the surface of the patient's body. In order to eliminate such a disadvantageous effect, a material for removing air is interposed between the probe and the surface of the skin. Therefore, there is a demand for a material which can be applied closely to both of the probe and the surface of the skin and has an ultrasonic properties (impedance) equivalent to that of the living tissue.

The temperature of the lesion site internally of the patient's body irradiated with an ultrasonic wave, radio wave or microwave must be maintained at a temperature of from 41.5°C to 43°C for a predetermined time when thermal therapy is applied for the medical treatment of cancer. Prior to the practical medical treatment, it is essential to learn the temperature rise in the internal sites in the patient's body under varying irradiation conditions (frequency, duration of irradiation, etc.). For such purpose, a material having thermal characteristics equivalent to those of the living tissues is demanded to prepare a model for simulating the living body.

It will be seen from the foregoing that there has been a demand for a material for simulating a living tissue to be used in medical treatment in which an ultrasonic wave or an electromagnetic wave is used. One example of the materials for simulating a living tissue is a fresh tissue of a killed animal extracted immediately after killing. However, it is difficult to have such a fresh animal tissue at every moment when it is demanded, and the electromagnetic and ultrasonic properties of the fresh animal tissue are abruptly changed even if such an animal tissue is stored in a cold place (H. F. Bowman, "Ann. Rev. Biophys. Bioeng.", 4, 43 (1975); F. K. Storm et al. "Int. J. Radiation Oncology Biol.

Phys.", 8, 865 (1982); and R. V. Damadian, U. S. Patent No. 3,789,832 (1974)). Accordingly, searching works for natural or artificial materials for simulating living tissues have been continued.

Since the living tissues generally have the electromagnetic and ultrasonic properties resembling those of water, it has been proposed to use water or a hydrogel having a high water content is used as a material for simulating a living tissue. For instance, a water bag (a pouch containing water) is placed on the surface of the skin for flattening the irradiated surface in the radiotherapy and a water bag is also placed on the surface of the skin for excluding the disturbance by air (for preventing reflection or diffusion and for matching the impedances) in the thermal therapy in which an electromagnetic wave or an ultrasonic wave is used. However, it is difficult to achieve stable operation by the use of a water bag due to defomation and dislocation of the bag. In order to avoid such disadvantages, the use of a high water content hydrogel, such as jelly, KONNYAKU or agar, has been proposed. Since they contain 96 to 98% of water, they have the properties resembling those of the living tissues, and yet they have tentative shape-retaining properties. However, jelly (gelatine) is so soft and easily deformed. Agar is fragile and easily broken, and KONNYAKU is greatly deformed or shrinked due to syneresis after it is molded. In addition, these known hydrogels are too high in water content as compared with those of the living tissues (the water content of soft living tissues ranges from 70 wt% to 80 wt%), and thus they are unsatisfactory in this respect. In order to prepare a material having properties closer to those of the living tissues, it has been proposed to replace a portion of water contained in the known hydrogel by n-propyl alcohol, glycerine, polyethylene glycol, sodium carbonate or graphite powders. However, the qualities of the materials from natural resources, such as agar and KONNYAKU, are unstable so that it is difficult to supply stable standardized products.

With the aim to preventing deformation of the aforementioned gelatine product, it has been tried to cross-link gelatin by formalin or glutaraldehyde. (E. L. Madsen et al, "Ultrasound in Med. Biol.", 8, (4) 381 (1982); E. L. Madsen et al, "Mag. Res. Imag." 1, 135 (1982); and E. L. Madsen et al, "Am. Assoc. Phys. Med.", 5, 391 (1978)). However, it was difficult to prepare a molded product of standardized quality due to uneven gelation or uneven cross-linking. High water content hydrogels prepared from polysaccharides, such as carrageenan or alginic acid, are inferior in mechanical strength similarly to agar.

Although polyacrylamide, one of the well known synthetic materials from which a high water content hydrogel may be prepared, has an advantage that a hydrogel having a controlled water content equivalent to those of the living tissues (70 to 85%) can be prepared therefrom, it is difficult to prepare a molded product of uniform quality therefrom due to difficulty in uniform gelation. The polyacrylamide gel has a further disadvantage that it is fragile and apt to be broken during the handling by pincettes.

Since it is difficult to prepare a material for simulating the living tissues by the use of a water bag or a natural or synthetic gel, it is a common practice to dip the diseased site in water. For example, when mammary cancer is irradiated with an ultrasonic wave, the patient is laid in the prone posture and the downwardly extending mamma is dipped in a water reservoir to ensure removal of air bubbles from the vicinity of the surface of mamma prior to exposure to the ultrasonic wave. Although it is possible to dip mamma, the limbs, the abdominal region, the chest and the neck, a large water reservoir is required to pose inconvenience in practical operation. The face, head, eye and other internal organs cannot be treated in such condition that they are dipped in water.

OBJECTS AND SUMMARY OF THE INVENTION:

Accordingly, a primary object of this invention is to provide a material for simulating a living tissue to be subjected to physical treatments (therapies in which an electromagnetic wave or an ultrasonic wave is used), the material being made of a high water content hydrogel which has ultrasonic and electromagnetic properties equivalent to those of living tissues and being soft and hardly fluidized and resistant to breakdown.

Another object of this invention is to provide such a material which contains 50 to 92 wt% of water to simulate a variety of living tissues including skin, lig. nuchae, liver and urinary bladder.

A further object of this invention is to provide such a material made of a high water content hydrogel and having a shape retaining property at 37°C and being moldable to have a desired shape and to be used for a long time while retaining the molded shape.

A further object of this invention is to provide a material for simulating a living tissue made of a hydrogel containing a large amount of fat to simulate a living fat tissue which contains a small amount of water.

A further object of this invention is to provioe a material having the properties substantially equivalent to those of the living tissue (specific inductive capaciy, conductivity, density, thermal conductivity, specific heat and hardness) having the same water content and thus satisfying the necessary conditions to be used as a material for simulating the living tissue in the physical treatment (irradiation with X-ray, gamma-ray, ultrasonic wave, neutron, laser, radio wave or microwave) in which electromagnetic wave and/or ultrasonic wave are used.

A further object of this invention is to provide a material for simulating a living tissue which is excellent in softness and rubber-like elasticity and can be closely fitted on the surface of the skin or the internal organ to be treated as far as it is molded to have a contour to profile the operated site, and which has a sufficient mechanical strength to be applied to the desired site repeatedly.

A further object of this invention is to provide a material for simulating a living tissue which may be sterilized by a sterilizing solution or irradiation with gamma-ray without being broken or deteriorated to be ready for application on the surface of the skin or an internal organ to be operated.

A further object of this invention is to provide a material for simulating a living tissue which is prepared from an aqueous solution of a polyvinyl alcohol only by thermal hysteresis at low temperature or through repeated freezing-thawing steps or processing under a reduced pressure without the use of any acids, alkali, chemical reagents or cross-linking agents harmful to the living tissue.

A further object of this invention is to provide a material for simulating a living tissue which does not contain any harmful material and which is inactive to the living tissue even if it is buried in a living tissue for a long time so as to be applied repeatedly on the surface of the skin or a variety of internal organs during the operation without causing foreign body reaction, cellular infiltration or inflammation.

A further object of this invention is to provide a material for simulating a living tissue which may be molded to have an internal cavity of desired shape or may be filled with a human bone, animal bone, plastic cylinder or tube to simulate a bone tissue or a canal tissue.

With the aforementioned objects in view, the present invention provides a material for simulating a living tissue for use in the electromagnetic and ultrasonic wave therapies, which comprises a hydrogel having a high water content and being prepared by a process comprising a casting step of casting an aqueous solution containing more than 8 wt% and not more than 50 wt% of a polyvinyl alcohol having a degree of hydrolysis of not less than 95 mol% and an average polymerization degree of not less than 1000 into a mold having desired shape and dimensions, a freezing step of cooling the cast aqueous solution to a temperature of not higher than - (minus) 10°C to obtain a cooled frozen mass, and a thawing step of thawing the cooled frozen mass, the freezing step and the thawing step being repeated up to eight cycles.

Also provided by the invention is a material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies, which comprises a hydrogel having a high water content and being prepared by a process comprising a casting step of casting an aqueous solution containing more than 8 wt% and not more than 50 wt% of a polyvinyl alcohol having a degree of hydrolysis of not less than 95 mol% and an average polymerization degree of not less than 1000 into a mold having desired shape and dimensions. a freezing step of cooling the cast aqueous solution to a temperature of not higher than - (minus) 10°C to obtain a cooled frozen mass, and a partial dehydration step of dehydrating the frozen mass in vacuum until the percentage dehydration rate reaches not less than 3 wt%.

DESCRIPTION OF THE INVENTION:

The present invention will now be described in detail.

According to the present invention, a material for simulating a living tissue and adpated for use in a physical therapy for treating a lesion site is prepared by a hydrogel having a specific formulation and a high water content.

The polyvinyl alcohol used in the invention should have a degree of hydrolysis of not less than 95 mol%, preferably not less than 98 mol%, and an average polymerization degree of not less than 1000.

In the present invention, an aqueous solution containing the aforementioned polyvinyl alcohol is prepared at the first step. The content of the polyvinyl alcohol in the solution should be in the range of more than 8 wt% and not more than 50 wt%.

In the next step of the process for preparing the hydrogel of the invention, the aqueous solution of the polyvinyl alcohol, as described above and defined in the appended claims, is cast into a mold suited for molding a desired shape for profiling a body model or a surface of a local site of human body. Then, the molded mass is cooled to be frozen, and the frozen mass is thawed to prepare a hydrogel having high water content to be offered to the aimed use. The hydrogel having a high water content, provided by the invention, may be subjected to repeated freezing and thawing cycles of

up to 8 times or cycles, when it is desired to prepare a material having a high mechanical strength. It is recommended that the freezing and thawing cycles are repeated from 2 to 8 times in consideration of the fact that the advantageous increase in hardness of the hydrogel with the increase in repeated cyclic treatments is saturated substantially by the 8 time repeated cycles and the increase of hardness or strength of the hydrogel is not so high after ninth cylce. (In this connection, reference should be made to Masao Nambu, "Polymer Application", 32 , 523 (1983).)

According to another aspect of the invention, the frozen mass may be partially dehydrated in vacuum after it is cooled to be frozen, in lieu of subjecting the same to the freezing and thawing steps. When a partial dehydration step effected in vacuum is adopted, the mechanical strength of the hydrogel is improved as the percentage dehydration rate is increased. It should be noted here that the wording "percentage dehydration rate" as used in this specification and claims is expressed by the percentage reduction of the weight of the cooled and solidified gel. However, it is not necessary to increase the percentage dehydration rate to an extremely high level to form a strong gel, and the percentage dehydration rate should be not less than 3 wt%, preferably in the range of not less than 3 wt% and not more than 35 wt%, to improve the shape-retaining property and machinability of the resultant hydrogel.

The partial dehydration in vacuum means that the hydrogel is dehydrated at some extent under a reduced pressure, and the level of reduced pressure is not particularly limited and ranges, for instance, not higher than 1 mmHg, preferably not higher than 0.1 mmHg and more preferably not higher than 0.08 mmHg. The mold is not particularly restricted as far as a molded product having a desired shape to profile a body model or a surface of a local site of a living body is prepared. The thickness (uniformity in thickness or thickness distribution) and the shape and dimensions of the molded product may be properly selected in compliance with the practical circumstances in the applied therapy in which a macrowave, radio wave, gamma-ray, X-ray, nuetron, laser beam or ultrasonic wave is used.

According to this invention, the water content of the hydrogel may be varied in consideration of the specific living tissue which is simulated by the hydrogel of the invention. The water content of the hydrogel is determined by the composition of the aqueous solution (or suspension) of polyvinyl alcohol used in the initial step. When the aqueous solution or suspension of polyvinyl alcohol is subjected to partial dehydration step after it has been frozen, the water content of the resultant hydrogel may be determined by calculating the amount of removed water derived at the partial dehydration step. The water content of a hydrogel which is prepared, without being subjected to partial dehydration, only by the freezing and thawing processings (or subjecting to repeated freezing and thawing cycles) may be easily calculated since the aqueous solution of polyvinyl alcohol used at the initail step has been gelled without removal of water therefrom.

Therefore, a material prepared in accordance with the present invention has a predetermined water content set to simulate the water content of a specific living tissue, such as skin (Water Content: 51 to 69%), ureter (Water Content: 58%), lig. nuchae (Water Content: 58%), achilles tendon (Water Coantent: 63%), tongue (Water Content: 60 to 68%), prostate (Water Content: 69 to 76%), lens (Water Content: 67 to 70%), liver (Water Content: 73 to 77%), stomach (Water Content: 80%), pancreas (Water Content: 75%), small intestine (Water Content: 80%), skeletal muscles (Water Content: 79 to 80%), uterus (Water Content: 80%), thymus (Water Content: 82%), bladder (Water Content: 82%) and kidney (Water Content: 78 to 81%). The material for simulating a living tissue prepared in accordance with the present invention is characterized by the fact that it has the electromagnetic properties (specific inductive capacity, conductivity, thermal conductivity, specific heat and hardness) and the ultrasonic properties (density and acoustic velocity) substantially agreed with those of the simulated living tissue. It is well known that the properties listed above are important parameters. The density (Density of Soft Living Tissue: 0.98×10^3 to 1.1×10^3 (kgm^{-3})) is an important parameter which affects the transmittance for X-ray and is in inverse proportion to the thermal diffusion coefficient and which affects the velocity, transmission, reflection and attenuation of the ultrasonic wave (H. S. Ho et al., "Trans. Microwave Theory. Tech.", MTT19, 224 (1971); and J. B. Leonard et al, "IEE Trans. Biomed. Eng." BME-31, 533 (1984)). The hardness or bulk modulus (Hardness of Soft Living Tissue: 2.6×10^9 Nm^{-2})) also affects the reflection, transmission and attenuation of the ultrasonic wave, and it is well known that acoustic velocity is in proportion to 1/2 power of the bulk modulus.

The specific inductive capacity (Specific Inductive Capacity of Soft Living Tissue: 64 to 200 at 10 MHz and 30 to 80 at 1 GHz) affects the attenuation, reflection and impedance of an electromagnetic wave. It is well known that the specific inductive capacity is in proportion to the thermal loss and that the transmission depth of an electromagnetic wave is in proportion to 1/2 power of the specific inductive capacity.

The conductivity (Conductivity of Soft Living Tissue: 0.5 to 0.9 ($ohm^{-1}m^{-1}$) at 10 MHz, 1 to 2 ($ohm^{-1}m^{-1}$) at 1 GHz and 10 ($ohm^{-1}m^{-1}$) at 10 GHz) affects the attenuation, transmission and impedance of an electromagnetic wave, and the transmission depth is in proportion to - 1/2 power of the conductivity.

The thermal conductivity (Thermal Conductivity of Soft Living Tissue: 0.5 to 1.3 ($Jm^{-1}s^{-1}K^{-1}$) at 1 MHz and 0.48 to 0.66 ($Jm^{-1}s^{-1}K^{-1}$) at 1 GHz) affects the generation and diffusion of heat, and the temperature of a living tissue is in proportion to 1/2 power of the thermal conductivity.

The specific heat (Specific Heat of Soft Living Tissue: 3.2 to 3.7 ($Jg^{-1}K^{-1}$)) also affects the generation and diffusion of heat, and the temperature of a living tissue is in proportion to - 1/2 power of the specific heat.

It is well known that the aforementioned properties of a soft living tissue are essentially determined by the water content of the living tissue (that is, the properties of living tissues are substantially approximate to those of water). The material for simulating a living tissue, provided by the present invention, has the aforementioned properties which are approximately agreed with those of the living tissue since it contains a large amount of water. The water content of the material provided by the present invention can be agreed with that of a specific soft living tissue (from 51 to 82 wt%, generally from 70 to 80 wt%) so that the material has the properties which are closer to those of the living tissue as compared with pure water. It is also well known that tissues enriched in lipid are present in the living body. In order to prepare a material for simulating a tissue enriched in lipid, a lipid is added to the initially prepared aqueous solution of polyvinyl alcohol followd by dispersing the same uniformly in the solution. For example, when it is desired to prepare a material for simulating a fat tissue containing 40% of water, an equivalent amount of lecithin or tristearin or another similar lipid is dispersed in an aqueous solution of polyvinyl alcohol having a water content of 80%. In preparation of a material for mimulating a tissue having a higher fat content, a solid fat, such as monostearin or tristearin, is heated to be liquefied and then the liquefied fat is added to an aqueous solution of polyvinyl alcohol which has been heated to a temperature of not lower than 70°C thereby to disperse the fat uniformly in the solution, prior to conducting the freezing step of the process of the invention, in order to preculde the risk that the shape-retaining property of the material for simulating the living tissue (gel) is deteriorated due to the presence of the fat. Through the operations as described above, a material corresponding to a fat tissue containing 15 to 30% of water may be prepared, and the thus prepared material has the electromagnetic and ultrasonic properties substantially agreed with those of a fat tissue of a living body.

According to a further important feature of the invention, two or more materials which are different from each other in water content may be bonded or joined together to form a composite material. A cyanoacrylate base adhesive may be used as the adhesive for preparing such a composite material, and it is more convenient that an aqueous solution of polyvinyl alcohol having a desired water content is applied on the surfaces to be joined and then the surfaces applied with the aqueous solution are joined, followed by additional freezing and thawing operations.

In the practice of the present invention, a hydrogel having a pertinent shape may be molded by the use of a mold having a desired mold cavity. Alternatively, a hydrogel having a certain desired shape is formed and then the hydrogel may be cut by scissors or a sharp cutter to have a final desired shape. A molded product for simulating a skeletal bone of a living body may be prepared by placing a human bone in the mold or by thrusting a heated iron bar through the molded hydrogel to form a cavity which is filled with a human bone. The hydrogel may be provided with a cavity or a cavity containing water which simulats, for example, trachea, esophagus, stomach, urinary bladder, lungs, nasal cavity, oral cavity, blood vessel, ureter or urethra. A hydrogel provided with such a cavity may be used as a model equivalent to a living tissue in the investigation for learning the reflection, scattering, absorption, transmission and multiple reflection of an electromagnetic or ultrasonic wave by the presence of air, a stagnant liquid or blood current.

The only material for forming a hydrogel, i.e. the gel forming ingredient, used in the present invention is the polyvinyl alcohol as defined in the claims. However, other ingredients or additives, which do not hinder gelation of the polyvinyl alcohol, may be present in the aqueous solution of polyvinyl alcohol similar to the aforementioned case where a fat is added, the amount of the coexisting additives being, for example, controlled in the range of not more than one half of the weight of the polyvinyl alcohol contained in the aqueous solution.

Examples of the additives which do not hinder gelation of the polyvinyl alcohol and may be contained in the gel forming solution are alcohols such as isopropyl alcohol, glycerin, propylene glycol and ethyl alcohol; proteins such as casein, gelatin and albumin; lipids such as lecithin, monostearin and tristearin; saccharides and polysaccharides such as glucose, agar and carrageenan; organic com-

pounds such as butyl-p-hydroxybenzoate, phthalocyanine blue and flavanthrone; and inorganic compounds, inorganic salts and organic salts such as nickel salts, copper salts, manganese salts, iron salts, graphite, activated carbon, silica-alumina, zeolite and calcium silicate. Well-known other additives for the precise adjustment of the electromagnetic property may also be added, the examples being polyethylene powders, aluminum powders, acetylene black, sodium carbonate and sodium chloride (A. W. Guy, "IEEE Trans. Microwave Theory Tech.", MTT-19, 205 (1971); J. B. Leonard et al, "IEEE Trans. Biomed. Eng.", BME-31 , 533 (1984); F. K. Storm et al., "Int. J. Radiation Oncology Biol. Phys.", 8, 865 (1982); E. L. Madsen et al,. "Med. Phys.", 5, 391 (1978); M. Michele et al., "Radiology", 134, 517 (1980); and P. E. Schuwert, "Ultrasonics", 275 (1982)).

One or more of the aforementioned additives may be directly, or in the form of an aqueous solution or suspension, added in the aqueous solution of polyvinyl alcohol under agitation so as to be dispersed uniformly therein, and then the aqueous solution or suspension may be subjected to the subsequent freezing and the other processing steps.

The material for simulating a living tissue, according to the present invention, may have a water content ranging from 50 wt% to 92 wt% to cover the varying water contents of various living tissues including skin and lig. nuchea (Water Content; 58 to 61%) and liver and urinary bladder (Water Content: 78 to 82%).

Although the material for simulating a living tissue, according to the invention, contains a large amount of water, it has a shape retaining property at 37°C to be molded to have a desired shape and to be used for a long time while retaining the molded shape.

A material containing a large amount of fat to simulate a living fat tissue and containing a small amount of water may also be prepared in accordance with the invention.

Since the material provided by the invention has the properties (specific inductive capaciy, conductivity, density, thermal conductivity, specific heat and hardness) substantially equivalent to those of the living tissue having the same water content, it satisfies the necessary conditions to be used as a material for simulating the living tissue in the physical treatments (irradiation with X-ray, gamma-ray, ultrasonic wave, neutron, laser beam, radio wave or microwave) in which an electromagnetic wave or ultrasonic wave is used.

The material provided by the invention is excellent in softness and reversible elasticity and can be closely fitted on the surface of the skin or the internal organ to be treated as far as it is molded to have a contour to profile the treated site, and also has a sufficient mechanical strength to be applied to the desired site repeatedly.

The material provided by the invention may be sterilized by a sterilizing solution, such as a solution of chlorhexidine or Osvan (Tradename), or irradiation with gamma-ray without being broken or deteriorated to be ready for fitting on the surface of the skin or an internal organ to be treated.

The material provided by the invention may be prepared from an aqueous solution of a polyvinyl alcohol only by thermal hysteresis at low temperature or repeated freezing-thawing or partial dehydration under a reduced pressure without the use of any acid, alkali, chemical reagent or cross-linking agent harmful to the living tissue. Accordingly, there is no need for removing any harmful ingredient from the molded product, and the molded product can be directly buried in a living body without causing foreign body reaction, cellular infiltration or inflammation for a long time and thus it may be applied repeatedly on the surface of the skin or a variety of internal organs during the operation.

The material provided by the invention may be molded to have an internal cavity of desired shape or may be filled with a human bone, animal bone, plastic cylinder or tube to simulate a bone tissue or a canal in the living body.

When the material for simulating a living tissue according to the present invention is applied to medical treatment, there are two methods. According to a first method, the material or hydrogel of the invention is applied to the surface of a human body so that the surface is flattened and then electromagnetic or ultrasonic wave is irradiated to the flattened surface. According to a second method, electromagnetic or ultrasonic wave is first irradiated to a phantom made of the hydrogel according to the invention to learn irradiation conditions such as frequency or duration of irradiation, and then electromagnetic or ultrasonic wave is irradiated to a human body under the irradiation conditions obtained from the phantom.

EXAMPLES OF THE INVENTION:

The present invention will now be described with reference to some examples thereof. In the following Examples, "%" stands for "% by weight" unless otherwise stated.

Example 1

A 29% aqueous solution (containing 0.9% of NaCl) of a polyvinyl alcohol having an average polymerization degree of 2.000 and a degree of hydrolysis of 99 mol% was cast into a casting mold for molding a cylinder having a diameter of 15 cm and a height of 12 cm. The cast mass was subjected to two cycle freezing and thawing operations to obtain a hydrogel having a high water content. The water content of the hydrogel was 70 to 71% which was approximate to that of the liver (Water Content: 70 to 77%), the lens (Water Content: 67 to 70%) and the prostate (Water Content: 69 to 76%) of a human body.

The electromagnetic properties of the thus obtained hydrogel were measured and compared with those of a liver resected from a dog immediately after the dog had been killed and also compared with those of pure water. The results were that the properties of the product of this Example were well agreed with those of the comparative living tissues, as will be seen from the following data.

Conductivity ($ohm^{-1}m^{-1}$, at 10 MHz): Example of the Invention: 0.7
Dog Liver: 0.6
Pure Water: 1.5

Specific Inductive Capacity (at 10 MHz) Example of the Invention: 70
Dog Liver: 64
Pure Water: 79

Density (kgm^{-3})

Example of the Invention: 1,040
Dog Liver: 1,030
Pure Water: 1,000

Thermal conductivity ($Jm^{-1}s^{-1}K^{-1}$) Example of the Invention: 0.8
Dog Liver: 0.7
Pure Water: 0.6

Specific Heat at Constant Pressure ($Jg^{-1}K^{-1}$) Example of the Invention: 3.7
Dog Liver: 3.5
Pure Water: 4.2

Bulk Modulus (dyne cm^{-2}) Example of the Invention: 2.5×10^{10}
Dog Liver: 2.6×10^{10}
Pure Water: 2.0×10^{10}

Example 2

314g of a 18.6% aqueous solution of a polyvinyl alcohol having an average polymerization degree of 1,000 and a degree of hydrolysis of 98 mol% was cast into a casting mold for molding a circular disk having a thickness of 1 cm and a diameter of 20 cm. The mold was then cooled to -30°C to form a frozen mass from which 22g of water was removed under a reduced pressure of 0.1 mmHg. Then, the temperature of the mold was returned back to the room temperature, and the dehydrated mass in the mold was discharged from the mold to obtain a circular disk shape gel having a water content of 80%. The thus prepared gel was stored in a sealed container. The water content of the gel was substantially equivalent to those (ranging from 78% to 81%) of skeletal muscles, small intestine, stomach, uterus and kidney of human body.

The thus prepared circular disk was put into a polyethylene film pouch and the pouch was sealed. After sterilizing the disk by irradiating with 3 Mrad gamma-ray, the pouch was opened and a small piece (10g) was cut from the disk. The small test piece was then transferred to a bouillon culture medium and cultured at 37°C for seven days. No microorganism was grown. The density of the gel was measured using another cut piece ($40 \times 40 \times 10$ mm) at 37°C to find that the density was 1.03×10^3 (kgm^{-3}) which was slightly higher than that of pure water and agreed with that of a soft living tissue (1.03×10^3 (kgm^{-3})). The acoustic velocity in the sample was measured by the hydro-ultrasonic wave total reflection angle detection system to find that the acoustic wave velocity was 1,600 (ms^{-1}) which was slightly higher than that in pure water (1,500 (ms^{-1})) and well agreed with that in soft living tissues (In the Liver: 1,600(ms^{-1}), In the skeletal Muscles: 1,600(ms^{-1}), In the Kidney: 1,560(ms^{-1}) and in the Skin: 1,600(ms^{-1})). It was thus confirmed that the hydrogel prepared by this Example was a material having an acoustic impedance (Density $\times$ Acoustic Wave Velocity) of $1,648 \times 10^3$ ($kgm^{-2}s^{-1}$) which was well agreed with the acoustic impedances ($1,600$ to $1,700 \times 10^3$ ($kgm^{-2}s^{-1}$)) of soft living tissues. The advantageous property of the material of this invention, as a material for simulating living tissues, should be appreciable when the acoustic impedance thereof

is compared with those of a silicone rubber (1.100 $\times$ 10^3 ($kgm^{-2}s^{-1}$)), polystyrene (2.460 $\times$ 10^3 · ($kgm^{-2}s^{-1}$)) and a butadine-acrylonitrile rubber (2,000 $\times 10^3$ ($kgm^{-2}s^{-1}$))

Then, the sample test piece was used to measure the output strength of ultrasonic wave based on the radiation power to find that an attenuation (absorption) factor was 3 $dBcm^{-1}$ (at 5 MHz). The value was closer to those of soft living tissues (Liver: 3 $dBcm^{-1}$, Kidney: 4.5 $dBcm^{-1}$) than to that of pure water (0.3 $dBcm^{-1}$). The advantageous property of the material of this invention, as a material for simulating living tissues in this respect, should be appreciable when the value was compared with those of a natural rubber (155 $dBcm^{-1}$), a silicone rubber (0.8 $dBcm^{-1}$) and a butadiene-acrylonitrile rubber (70 $dBcm^{-1}$).

Example 3

A 25% aqueous solution of a polyvinyl alcohol having an average polymerization degree of 2,600 and a degree of hydrolysis of 99 mol% was cast in a casting mold for molding a cylinder having a diameter of 30 cm and a height of 30 cm, and the cast mass was frozen at - 40°C, followed by thawing, to prepare a hydrogel. The hydrogel had a modulus of elasticity (10^5 Nm^{-2}) of 0.4 and a hardness resembling that of smooth muscle, and it did not collapse even when it had been held under a compressive pressure of 50 $kgcm^{-2}$ for 30 minutes although it had a free and rubber-like deformability. The results showed the advantage of the material prepared in accordance with this invention contrary to the hydrogels prepared from agar and carrageenan. The latter-mentioned hydrogels easily collapsed under the same conditions. The tensile strength of the hydrogel of this Example was 30 $kgcm^{-2}$.

Example 4

Generally following the procedures as described in Example 3, ten test pieces of hydrogel (30 $\times$ 30 mm) having a thickness of 0.3 mm were prepared.

The test pieces were sterilized with chlorhexidine, and rinsed with a physiological saline solution under germ-free condition. One test piece was implanted under the skin of the back of a rabbit. After the lapse of 16 months, the surrounding living tissues were inspected to find no foreign body reaction such as inflammation or cellular infiltration and no excessive growth of connective tissue.

Likewise, an adult mongrel dog was intubated under general anesthesia, and the left fourth intercostal space of the dog was cut and opened for removing a portion of the pericardium by about 2 cm under controlled respiration, whereby a defect was made and the aforementioned sterilized test piece was sutured on the defect with Tevdek string. The results of anatomic inspection, after the lapse of one year, revealed that no abnormality was found in the vicinity of the hydrogel prepared by the invention and incorporated in the dog. Similarly, in a case where the same test piece was sewn to pleura of an adult dog, no foreign body reaction or adhesion was found when the operated portion was inspected after the lapse of seventeen months.

The inside surface of the knee joint of a rabbit (Body Weight: 2.5 kg) was opened along the longitudinal direction by 3 cm and the inside of the quadriceps femoris muscle was opened along the longitudinal direction. Then the patella of the rabbit was dislocated outwardly, and the lipid tissue at the front portion of the knee joint was removed while the knee joint was kept in the bent position. After cutting the cruciate ligament, the capsula articularis other than the back capsula articularis and the semilunar plate were resected. Then, the cartilage of the femur joint was deleted, and the aforementioned sterilized test piece was inserted and fixed on the face of the femur joint in place of the deleted cartilage, and then the knee joint was fixed in such condition that the joint was bent to subtend an opening angle of 150 degrees by applying a plaster bandage from the upper portion of the femur to the foot. The plaster bandage was removed after the lapse of four weeks. At that time, no rubefaction or local pyrexia was found although a slight swelling was observed at the joint, and the healing by first intention was satisfactory with no secreting fluid. The knee joint was bent to subtend about 120 degrees and the protective limping motion was observed. The movable anglular range by forcible bending was 150° to 90°. A histological specimen was excised and fixed by formalin, encapsuled with paraffin, dyed with haematoxylineeosine stain and then dyed with Mallory-azan stain. The thus treated specimen was inspected through a microscope to confirm that the molding joint face of the femur was covered by the connective tissue and that there was found no reactive osteogenesis and no inflammation in the bone-marrow. From the results of the inspection, it was confirmed that the hydrogel prepared by the present invention was excellent in adaptability to living tissues.

Hairs were removed from the scalp of an adult mongrel dog having a body weight of 17 kg and put under general anesthesia by intravenous injection of pentothal sodium. The scalp of the right top was cut by 7 cm along the longitudinal direction.

and the temporal muscle was peeled off. Then, the parietal bone was pierced using a drill and a defect having the dimensions of a hen's egg was formed through the parietal bone using a bone forceps. The dura mater encephali was resected to form an opening of 1.5 x 2 cm. The opening was covered by the aforementioned hydrogel piece (having a high water content), with the four corner portions being sutured, and then the M. temporalis and the scalp were sewn together.

After the lapse of 8 months, the dog was killed and the hydrogel piece and the dura mater encephali and the parenchyma surrounding the hydrogel piece were excised. The results of visual observation and the results of microscopic observation of a specimen dyed with haematoxylin-eosin stain revealed that the hydrogel did not adhere to the surface of the brain. Although the surface of the hydrogel was encapsulated by fibrous tissues, no substantial adhesion thereof to the pia mater encephali was found and cellular infiltration and growth of Glia cells were not found.

The chest of an adult mongrel having a body weight of 13 kg and put under general anesthesia by intravenous injection of pentobarbital was opened, and a major portion of the pericardium at the left ventricle side was resected so that only the marginal rims for suturing were left. The thus formed defect of the pericardium was repaired by the use of the aforementioned hydrogel membrane.

Test specimens excised from the repaired portion of the sacrificed body after the lapse of 8 months were observed visually and through an optical microscope and scanning type electron microscope. The results were that the hydrogel had not adhered to the tissues of the heart and the surface of the hydrogel membrane was covered by an endothelial tissue and was smooth. No histological cellular reaction was found, and a thin endothelium tissue was found at the side facing to the heart.

The chest of an adult mongrel having a body weight of 15 kg was opened and a defect was formed at the muscular portion of the diaphragm. and the thus formed defect was repaired by the aforementioned hydrogel membrane. A test specimen excised from the repaired portion of the sacrificed body after the lapse of 8 month was inspected to reveal that the repairing hydrogel did not adhere to the tissue of the lung. The hydrogel piece was encapsulated by fibrous tissues, but no histological reaction was found.

Example 5

A molded product was prepared by casting a 15% aqueous solution of a polyvinyl alcohol having an average polymerization degree of 1.200 and a degree of hydrolysis of 99% into a casting mold for molding an arcuated membrane having a radius of curvature of 8 mm, a uniform thickness of 0.2 mm and a diameter of 13 mm, followed by two cycle freezing and thawing processings. The thus prepared molded article was fitted on the cornea of an eye of a volunteer for 10 hours. After removing the hydrogel product, the cornea was dyed with the fluorescein stain and inspected through a slit lamp microscope to find that the cornea had no portion stained by the dye. It should be apparent from the results that the material for simulating a living tissue prepared in accordance with the present invention is excellent in adapatability to the living body, and that it is well suited for use in the condition of contacting the living tissue in view of the combined consideration of the results obtained in this Example and the result obtained in Example 4.

Claims

1. A material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies, which comprises a hydrogel having a high water content and being prepared by a process comprising a casting step of casting an aqueous solution containing more than 8 wt% and not more than 50 wt% of a polyvinyl alcohol having a degree of hydrolysis of not less than 95 mol% and an average polymerization degree of not less than 1000 into a mold having desired shape and dimensions, a freezing step of cooling the cast aqueous solution to a temperature of not higher than - (minus) 10°C to obtain a cooled frozen mass, and a thawing step of thawing said cooled frozen mass, said freezing step and said thawing step being repeated up to eight cycles.

2. A material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies, which comprises a hydrogel having a high water content and being prepared by a process comprising a casting step of casting an aqueous solution containing more than 8 wt% and not more than 50 wt% of a polyvinyl alcohol having a degree of hydrolysis of not less than 95 mol% and an average polymerization degree of not less than 1000 into a mold having desired shape and dimensions, a freezing step of cooling the cast aqueous solution to a temperature of not higher than - (minus) 10°C to obtain a cooled frozen

mass, and a partial dehydration step of dehydrating the frozen mass in vacuum until the percentage dehydration rate reaches not less than 3 wt%.

3. The material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies as claimed in claim 2, wherein said partial dehydration step is effected at a pressure of not more than 1 mmHg.

4 . The material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies as claimed in claim 2 or 3, wherein said cooled frozen mass is dehydrated until the percentage dehydration rate reaches to a level ranging from 3 wt% to 35 wt%.

5. The material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies as claimed in any of the claims 1 to 4, wherein said aqueous solution contains an additional ingredient which does not hinder gelation of said polyvinyl alcohol in an amount of not more than one half (1/2) of the weight of said polyvinyl alcohol contained in said aqueous solution.

6. The material for simulating a living tissue for use in the electromagnetic wave and ultrasonic wave therapies as claimed in claim 5, wherein said additional ingredient is selected from the group consisting of isopropyl alcohol, glycerin, propylene glycol, ethyl alcohol, casein, gelatin, albumin, lecithin, monostearin, tristearin, glucose, agar, carrageenan, butyl-p-hydroxybenzoate, phthalocyanaine blue, flavanthrone, nickel salts, copper salts, manganese salts, iron salts, graphite, activated carbon, silica-alumina, zeolite, calcium silicate, polyethylene powders, aluminum powders, acetylene black, sodium carbonate and sodium chloride.

7. A phantom adapted for use in the electromagnetic and ultrasonic wave therapies as claimed in any of the claims 1 to 6.

8. The phantom adapted for use in the electromagnetic and ultrasonic wave therapies as claimed in claim 7, wherein said phantom contains 50 to 92 wt% of water.

9. The phantom adapted for use in the electromagnetic and ultrasonic wave therapies as claimed in claim 7, wherein said hydrogel further contains a lipid.

10. The phantom adapted for use in the electromagnetic and ultrasonic wave therapies as claimed in claim 7, wherein a plurality of said phantoms having different water contents are joined together.